Two of These or Two of Those?

Symmetrically dividing neuroepithelial cells may produce two daughters that are both proliferating or both postmitotic, as highlighted by Zigman et al. in this issue of *Neuron* and Sanada and Tsai in a recent issue of *Cell*. Here, I will attempt to offer a simple explanation why these results may be so different.

If Danny DeVito had an identical twin, he would probably be shorter than Hulk Hogan's hypothetical identical twin. A symmetrical division of one neural progenitor produces a pair of cells that are like identical twins. A symmetric division of another neural progenitor produces a completely different pair of cells. These pairs are different because their parents are different, Danny's or Hulk's.

To help understand how this analogy might be relevant to the difference between the Zigman et al. (2005) and the Sanada and Tsai (2005) results in the mouse, it may first be useful to look at symmetrical and asymmetrical cell divisions in the *Drosophila* central nervous system. *Drosophila* neuroblasts arise from symmetrical divisions of the cells in the horizontal plane of the neurogenic region of the blastoderm. Individual cells in this region, selected as neuroblasts, delaminate from the epithelium and then begin a series of asymmetric apicobasal divisions producing at each division an apical neuroblast (NB) and a basal ganglion mother cell (GMC). The machinery involved in these asymmetric divisions involves proteins that organize into a complex at the apical cortex of the neuroblast (Kaltschmidt and Brand, 2002; Roegiers and Jan, 2004; Wang and Chia, 2005). A key component of this complex is the membrane-associated Inscuteable (Insc) protein. Insc binds to Par-3/Par-6/aPKC and Partner of Inscuteable (aka Pins). Pins then binds to Gαi, leading to the local activation of heterotrimeric G proteins, particularly G$\beta\gamma$, that attracts one of the two centrioles, thus orienting the plane of division along the apicobasal axis (David et al., 2005; Izumi et al., 2004; Wang and Chia, 2005; Yu et al., 2003).

The different fates of the apical NB and the basal GMC are tied to the differential inheritance of cytoplasmic determinants, Numb and Prospero, located at the basal pole of the parental NB at the moment of cytokinesis. Numb is a negative regulator of the Notch pathway, and Prospero is a homeodomain transcription factor (Knoblich et al., 1995). The asymmetric inheritance of these two proteins differently affects the fates and proliferative potentials of the NB and the GMC. GMCs do not divide apicobasally; they divide in the horizontal plane to produce two postmitotic daughters.

The *Drosophila* situation is remarkably similar to neuroepithelial cells in the mammalian cortex. At early stages, these cells tend to divide symmetrically, giving rise to two dividing progenitor cells, but as neurogenesis proceeds, some neuroepithelial cells begin to divide asymmetrically: one neuroepithelial progenitor and one differentiated neuron. Toward the end of neurogenesis, symmetrical cell divisions predominate again, producing two postmitotic neurons (Cai et al., 2002). Time-lapse observations of neuroepithelial cells in organotypic slices of the developing mammalian cortex show that divisions along the horizontal plane produce two cells that stay in contact with the ventricular surface, whereas more apicobasal divisions produce a basal daughter that migrates away from the ventricular surface while the other daughter remains in contact, consistent with it retaining a neuroepithelial fate (Chenn and McConnell, 1995).

These interesting similarities between *Drosophila* and mammalian neurogenesis have attracted vertebrate workers to search for homologs of the *Drosophila* genes involved in asymmetric cell divisions (reviewed in Huttner and Kosodo, 2005). In the two papers highlighted in this preview, Sanada and Tsai (2005) interfere with G$\beta\gamma$ and ASG3, a mammalian homolog of Pins, while Zigman et al. (2005) clone and then interfere with a mammalian Insc homolog. Sanada and Tsai (2005) used the carboxy terminus of the β-adrenergic receptor kinanse (βARK-ct) to block G$\beta\gamma$ signaling in the mouse cortex, which leads to the loss of spindle orientation along the apicobasal axis. Neuroepithelial cells misexpressing βARK-ct not only have more planar divisions, they also exit the cell cycle early and produce pairs of neurons (Figure 1). In vivo, these overexpressing βARK-ct cells migrate away from the ventricular zone and into the intermediate zone and cortical plate, indicating that they give rise to early differentiating neurons. They obtain similar results by knocking down the Pins homolog, ASG3, by electroporation of RNAi. Zigman et al. (2005) examine the retina rather than the neocortex. They show that the mInsc protein localizes to the apical pole of retinal progenitors and that knocking down mInsc using retroviral infection of short hairpin RNAi causes retinal progenitors to divide preferentially in the horizontal plane and produce larger clones. If allowed to mature in vivo, these clones show an excess of bipolar cells, the last-born neural cell type in the mouse retina.

The question is why are the final results of these two studies so different? One possibility is that it has something to do with numb. It is well known that the lateral inhibition through the Notch pathway is responsible for generating differential fates at many points in a cell lineage. The most well known example is the *Drosophila* sensory organ precursor lineage, where loss of numb or interference with Notch signaling at different points leads to both daughters adopting symmetrical fates either as spIIb progenitors, sensory neurons, or bristle shaft cells, depending on where in the lineage tree Notch signaling is disturbed (Schweisguth et al., 1996). The apical localization of mammalian numb, a regulator of Notch signaling, may thus have strikingly different effects on cell fates depending where in the lineage it is differentially inherited. Mouse numb knockouts suggest that numb is essential for the cortical neuroepithelial

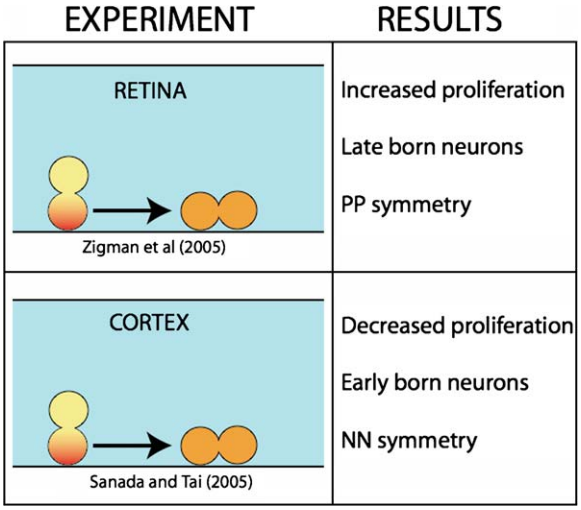

Figure 1. Different Symmetries from Similar Experiments

The top panel shows the Zigman et al. (2005) experiment in the mouse retina where the apical complex (red) is compromised by RNA interference with mInsc, and the Sanada and Tsai (2005) experiment in the mouse cortex where the apical complex is compromised by RNAi to ASG3 is shown below. In both cases, there is a reduction in apicobasal divisions in favor of divisions in the horizontal plane. The effect of this is a change of fate in both cases, but in the retina it is an increase in PP symmetry, while in the cortex it is an increase in NN symmetry.

cells to remain in a progenitor sate (Petersen et al., 2002). Studies in the rat retina late in neurogenesis, however, show that the inheritance of numb does not favor cells remaining in the cell cycle. In horizontal divisions, where both daughters inherit numb, they often both differentiate into the same type of cells, such as photoreceptors, a fate that is also promoted by overexpression of numb, whereas the asymmetric distribution of numb in the these cells correlates with different postmitotic fates (Cayouette and Raff, 2003). Numb is only one of many determinants that could be symmetrically or asymmetrically partitioned according to the orientation of cell division. Thus, it is not much of a leap to imagine that the symmetric versus asymmetrical inheritance of numb, or perhaps other determinants, might have very different consequences in the retinal versus neocortical lineages. The key point here is that the featured studies show that the orientation of division does have a role in determining cell fate in the developing mammalian nervous system, as it does in *Drosophila*. But that role is different in different lineages. Thus, decreasing apicobasal division increases symmetrical fates, even though these fates might be very different in distinct regions of the nervous system that are undergoing different (Danny DeVito- or Hulk Hogan-generating) lineage programs.

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Local Axon Guidance in Cerebral Cortex and Thalamus: Are We There Yet?

Normal brain function requires the development of precise connections between thalamus and cerebral cortex. In this issue of *Neuron*, Cang et al. and Tori and Levitt argue that EphA/ephrin-A signaling in the target tissue guides sensory thalamic axons to the correct cortical area, and sensory cortical axons to precise thalamic targets. Although EphA/ephrin-A signaling organizes sensory maps within areas, and thalamocortical axons in the internal capsule, both papers argue that each developmental event is dissociable from the others.

Higher functions of the mammalian brain, including perception, planned movement, and cognition, rely on a complex interaction between cerebral cortex and the thalamus. Still unanswered is the question of how the anatomical substrate for this interaction, a highly patterned reciprocal innervation, is established in development.

In this issue of *Neuron*, two studies make significant advances toward an answer (Torii and Levitt, 2005; Cang et al., 2005). Torii and Levitt conclude that axons from sensory cortex find a precise target in the thalamus by responding to local levels of ephrin-A5. Cang and colleagues provide evidence that ephrin-A2, -A3, and -A5 are required to position primary visual cortex (V1) in the cortical plate as well as to direct formation of a visuotopic map in V1. Perhaps just as significant, the latter investigation exemplifies a new type of study, combining genetic manipulation of development with optical imaging of an altered cortical area map.